

AN OVERVIEW OF DIABETES MELLITUS

An Honors Thesis (HONRS 499)

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Introduction

Diabetes mellitus is the most common endocrine disorder. According to the American Diabetes Association (ADA), this disease afflicts more than 10 million persons in the United States alone. During the coming year, it is estimated that another 750,000 people will be diagnosed with this disease. Since 1932, Diabetes Mellitus (DM) has ranked among the 10 leading causes of death in the United States. Given these statistics, it would only be wise to examine ways in which we can control and even prevent the onset of this debilitating disease.

The medical community and some of the general public know that this disease can be controlled with medication and diet. Besides this, research has shown repeatedly that regular physical exercise can improve the health and disease status of diabetics, along with preventing the onset of the disease in others. (Porte & Rifkin, 1990) In order to use this information to our benefit, we must make more of the public aware of this disease and the magnitude of it.

I have examined this disease not only in the text books I have read but in real life situations. I have witnessed the effects of years of misunderstanding on the patient level. Yet, I have, also, seen the effects of proper medical treatment, education and regular aerobic exercise on the disease process. In an attempt to increase the awareness and knowledge that the general population has of this disease and the effects of regular aerobic exercise, I have decided to write the following paper on diabetes mellitus.

Definitions and Classifications

Diabetes mellitus (commonly called diabetes) can be associated, in general, by problems in the control of blood glucose levels that result in the elevated concentration of glucose in the blood (hyperglycemia) and problems in the regulation of insulin. (Porte & Rifkin, 1990) It

represents a syndrome of insulin deficiency that can be caused as a result of heredity and/or environmental factors. Along with the more apparent hyperglycemia, other metabolic abnormalities are present that are linked with the hyperglycemia. Such abnormalities include disturbances in the metabolism of carbohydrates, fats, and proteins often linked with absolute or relative deficiencies in insulin secretion and/or insulin action.

Due to the search for more knowledge, more is being learned about diabetes and the disease process of it. One change that can be noted is the classification of the disease. A short time ago diabetes was grouped into two categories: juvenile diabetes and adult onset diabetes. However, the line between the two was not always cut and dry. It was difficult to determine what type of diabetes the patient had. A modification had to be made in the classification of diabetes, in order to more efficiently represent the disease type. This change resulted in the new classification of Type I, or insulin dependent (IDDM) and Type II, or non-insulin dependent (NIDDM). There are also more ways in which diabetes can be classified, but these are the major ones.

IDDM, as the name implies, is dependent on insulin supplementation. This supplementation is necessary to avoid life threatening complications and maintain the life of the diabetic. This disease is often characterized by a sudden onset of symptoms that result from a deficiency of insulin production by the pancreas. (Huether & McCance, 1990) In IDDM, actual death of the beta cells in the islets of Langerhans is reported. (Arky, 1983) This, in turn, leads to a deficit in insulin production and action. This deficiency in insulin action leads to metabolic consequences.

IDDM is likely to be categorized as having the more "classic" symptoms associated with

diabetes. These metabolic symptoms include excessive thirst (polydipsia), excessive urination (polyuria), unsatisfied hunger (polyphagia), weight loss, cessation of growth among the young, irritability, and drowsiness. (Pickup & Williams, 1994) Insulin is used in an effort to replace the insulin that is lacking in the body which helps to utilize the excess glucose. Uncontrolled diabetes can have such implications as glucose in the urine (glycosuria), excessive levels of glucose in the blood (hyperglycemia), and high levels of ketone bodies in the blood (ketosis). (Arky, 1983) Insulin is used to treat IDDM by replacing insulin levels and thus, utilizing the excess glucose.

IDDM is the most prevalent form of diabetes among children and young adults. It can occur at any age, but is more widespread in the young. IDDM develops more frequently during adolescence with its peak onset being between the ages of 11-13 and then after the age of forty. Only about 10% of all diabetic patients have this form of diabetes.

Although the relationship between diabetes and heredity and the environment is still being examined, a link between race and the susceptibility of developing IDDM has been established. People of northern European origin are more likely to be diagnosed with IDDM. The disease has a much lower incidence among people of Oriental or native American heritage. As far as heredity and IDDM, a clear correlation between the two has not yet been established.

The second type of diabetes, which is classified as Type II (NIDDM), accounts for nearly 90% of all diagnosed cases. (Nieman, 1995) NIDDM may have the classical symptoms associated with it, as in IDDM. However, it is more apt to be asymptomatic. An incidence of hyperglycemia in people with NIDDM is noted, also. Nevertheless, insulin treatment is not prescribed for the same reason as in IDDM. Rather, insulin treatment is used to control the glucose levels in the blood, and is not needed to maintain the life of the patient on an immediate

basis, as it is in IDDM.

NIDDM results from impaired pancreatic beta cells and abnormalities on cell surfaces or within the cell which leads to diminished cell sensitivity to insulin. (Reference, 1989) Rather than actual death of the beta cells that is associated IDDM, only impairment is noted. This results in hyperglycemia and the other metabolic symptoms mentioned above. Unfortunately, the first signs of the disease may be such complications as neuropathy or atherosclerotic heart disease.

There appears to be a more established link between heredity and NIDDM. However, the more apparent link seems to be between NIDDM and obesity. Nieman refers to this phenomenon as "diabesity". (1995) It has been shown that people who are 50% or more over their desirable body are five times more likely to be diabetics than those of normal weight. Frequently the diabetes may occur as a triad--hyperglycemia, obesity, and hypertension. (Pickup & Williams, 1994) All of which present an increased risk for heart disease. Although obesity may intensify the cells' resistance to insulin and may precipitate hyperglycemia, NIDDM can develop in the absence of obesity.

Pathophysiology

Diabetes is a syndrome that encompasses many etiologies and abnormalities. Yet, they all share one common factor: hyperglycemia. Diabetic symptoms may result from insulin deficiency or from insulin resistance that renders insulin ineffective. The abnormality may be caused by one of many factors. Factors may include an abnormality in the beta cells in the islets of Langerhans, in the circulation, in the cell membrane, or in the target cells.(Huether & McCance, 1990) IDDM is usually marked by a defect in insulin secretion due to a dead or dying beta cell. NIDDM may result from a defect occurring at any point in insulin secretion, circulation, or

peripheral action. (Pickup & Williams, 1994)

In trying to understand the pathophysiology of diabetes, we must first be aware of what insulin is and does in the body. Insulin is a hormone secreted by beta cells in the islets of Langerhans in the pancreas. This hormone is responsible for regulating glucose levels in the body. It is also the primary hormone controlling the storage and metabolism of carbohydrates, proteins, and fats. The body stores and metabolizes nutrients largely through insulin's control, with glucose included. In diabetes, the impairment of carbohydrate metabolism often coexists with impaired fat and protein.

After a meal, minimal insulin deficiency leads to elevated blood glucose levels because not enough of the hormone is available to enable cells to utilize the extra glucose. As in diabetics, severe insulin deficiency has the same effect. Without insulin, glucose cannot enter the cells. Since glucose is a major source of cell energy, the cells are deprived. They turn to other pathways of metabolism to meet their energy needs. Therefore, protein and fat breakdown occurs because of the lack of insulin.

An acute insulin deficiency may lead to diabetic ketoacidosis (DKA) by altering carbohydrate, fat, and protein metabolic pathways. (Arky, 1983) If this is not corrected, DKA will progress to diabetic coma and death. However, IDDM is the type that is more likely to be linked with this progression. Yet, DKA is still a risk in NIDDM. Thus, it should not be taken lightly.

Insulin is not the only hormone involved in diabetes. Other hormone frequently accompany the insulin deficiency. These hormones include glucagon, cortisol, catecholamines, and growth hormones. Each of these hormones counteracts the insulin and thus promotes

hyperglycemia. Glucagon is the primary hormone involved with the insulin. The body does not stop secretion of this hormone even with low levels of insulin in the body. One would come to assume that because of the way the body works, hyperglycemia would suppress the secretion of glucagon. Due to the low levels of insulin in the body, the glucagon is not suppressed. Therefore, the insulin deficiency needs to be corrected by medical measures. Again, this type of insulin shortage is more commonly coupled with IDDM rather than NIDDM.

As I mentioned before, insulin is produced by the beta cells in the islets of Langerhans. It has been shown that in people with diabetes the beta cells are in some way interrupted thus disturbing the production and secretion of insulin. (Osterby, 1983) It has been shown that in a person with IDDM the beta cells are destroyed. Although, hyperglycemia can occur, 80% to 90% of the insulin-secreting beta cells in the islets of Langerhans must be destroyed. (Huether & McCance, 1990)

The destruction of the beta cells in IDDM is marked by a presence of islet cell antibodies (ICA). ICA is present in up to 85% of newly diagnosed insulin dependent diabetics. (Pickup & Williams, 1994) Although the functional role of ICA has yet to be determined, it appears to play a role in the destruction of such tissues. ICA is only found in about 5% of non insulin dependent diabetics.

Other theories that explain the etiology of IDDM propose that it involves an immune reaction, a viral disease, or inherited susceptibility combined with environmental factors. Porte & Rifkin have shown that IDDM involves an autoimmune response that destroys the beta cells gradually. (1990) Although no direct evidence of such a mechanism exists, the stimulus is thought to be a virus or a group of viruses. The genetic link is still being established in IDDM.

In contrast to IDDM, beta cells in NIDDM are not destroyed. They may still produce insulin, but they do so at a sluggish rate. Besides delayed insulin secretion, some subsets of NIDDM manifest insulin resistance in tissues such as muscle, liver and adipose tissue.

As for NIDDM, the pathophysiology is not as clear. Although, the understanding of the pathogenesis of the disease has advanced considerably in the recent years. The pancreatic changes in NIDDM are nonspecific. NIDDM is usually caused by some gene-environmental interaction. In the diabetic with NIDDM an inherited secretory deficiency of insulin and an excess of glucagon may contribute to the disease process. However, the risk factor that is most closely associated with NIDDM is obesity.

In the obese person, insulin has a decreased ability to influence glucose uptake and metabolism in the liver, skeletal muscles, and adipose tissue. Many theories have been proposed as to why the obese person is more likely to have an onset of NIDDM. These theories cover a great range of ideas. One theory states that a decreased number of insulin receptor sites on the plasma membrane will result in decreased insulin binding which results in a sensitivity to insulin. (Dunn, Petri, & Raskin, 1980) Another theory that more clearly states a relationship between diabetes and obesity is the one which implies that overeating leads to an increase in the insulin in the body which, in turn, necessitates the development of peripheral insulin resistance to protect against hyperglycemia. (Pickup & Williams, 1994) It is important to remember that obesity alone is insufficient to cause NIDDM. However, genetic predisposition and some impairment in the secretion of insulin is necessary for the development of NIDDM. In any case, the mechanism which is responsible for the cause of NIDDM may be reversed through weight loss.

Complications Associated with Diabetes Mellitus

The diabetic person must take great care in the management of their disease. First and foremost, the diabetic must control their glucose levels through such means as diet, medication, and exercise. This is not an easy task to accomplish. As any diabetic can tell you, complications will arise. Most of the time they can be prevented, but one must be aware that they exist.

There are two categories that exist: acute and chronic. Acute means that the complications are short term and almost always reversible with correct treatment, if identified correctly. Chronic complications, on the other hand, are generally long term and permanent. There are three main acute complications that arise from uncontrolled diabetes, of which include hypoglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemia nonketotic coma. (Nieman, 1995)

Hypoglycemia is a lowered blood glucose level. In general, hypoglycemia occurs when blood glucose levels fall below the level of 45-60 mg/dL. (Porte & Rifkin, 1990) This can result from too much insulin, too little food or excessive physical activity. At low levels, the person may exhibit signs of impairment which may be physical and neurological. Due to the fact that the brain is dependent on the oxidation of glucose for energy, neurological symptoms are almost always present to some extent. When the blood glucose levels fall, the brain is unable to function and symptoms of hypoglycemia ensue. The symptoms are not the same for every individual, but they remain consistent for each person. The symptoms of hypoglycemia can range from pallor, tachycardia, sweating, nausea, anxiety, and hunger. In adults, sweating is often an especially prominent symptom of hypoglycemia. Neurologic symptoms have been identified, but not limited to blurred vision, headaches, behavioral changes, and disturbed mentation. Hypoglycemia may cause permanent neurologic damage.

Hypoglycemia is sometimes noticed in non-diabetics but is most often noticed in people with diabetes, particularly IDDM. In any case the safest treatment when hypoglycemic conditions occur is to provide some form of glucose. If this is not done, the person may experience convulsions, or go into a diabetic coma. The end result, if left untreated, could be death.

Diabetic ketoacidosis is a condition that results from an insulin deficiency. Ketoacidosis most often occurs in stressful situations, such as infections, trauma, surgery, myocardial infarction, or emotional stress. Inadequate insulin levels in the blood and tissues sets off a chain of metabolic events.

The first effect of insulin deficiency is a decrease in the utilization of glucose. The outcome will be an accumulation of glucose in the blood due to the fact that the glucose can not enter the cell without insulin. When the accumulated glucose exceeds the renal threshold, it spills into the urine. The excess urine glucose acts as an osmotic diuretic. The final effect is increased thirst with dehydration following.

At the same time, fats are broken down to supply energy to the glucose-starved cells, and accelerated gluconeogenesis, reproduction of glucagon, is occurring. The problems lies with the rate at which the fatty acids are broken down compared to the rate at which they are utilized. Since the fatty acids are broken down faster than they can be used, ketones, end products of fat metabolism, form in the liver, accumulate in the blood stream and accelerate metabolic acidosis. Ordinarily, ketones used by the brain or skeletal muscles as an energy source will regenerate bicarbonates to counteract their acidity. However, the increase in ketones production causes a loss of bicarbonate and other body buffers, resulting in the subsequent development of metabolic acidosis.(Reference, 1989) Symptoms of DKA can include, but are not limited to Kussmaul

respirations (hyperventilations in an attempt to correct the acidosis), postural dizziness, central nervous system depression, and abdominal pain. (Arky, 1983) The best treatment for DKA is the administration of low-dose insulin in an attempt to lower blood glucose levels.

Hyperosmolar hyperglycemic nonketotic coma (HHNK) is basically DKA without the ketoacidosis. In this condition, the patient has enough insulin to inhibit lipolysis. Unlike hypoglycemia and DKA, HHNK is typically observed inpatients with NIDDM. The condition is a life-threatening emergency with a high mortality rate.

Chronic complications generating from years of diabetes are fairly common in the diabetic world. Before the discovery of long-term insulin, chronic complications were basically unheard of because of the short survival time. Now, long-term survival is a rule. As a result, chronic complications have become important. There are many chronic complications that can be discussed, each with its own sub-division. Yet, the major ones in which I am going to address are diabetic neuropathy, microvascular disease, and macrovascular disease. These are the most common and widely noted complications.

Although diabetic neuropathy is probably the most common complication in diabetes, it is very poorly understood. The overall presence of diabetic neuropathy is uncertain but appears to parallel the duration and severity of the hyperglycemia in both IDDM and NIDDM. It is rarely found before the fifth year of diabetes, except in NIDDM due its asymptomatic nature. It will ultimately effect up to 50% of patients with long term diabetes.

Diabetic neuropathy affects many structures and gives rise to broad range of symptoms, including the common peripheral neuropathy. Peripheral neuropathy is the most abundantly noted type of neuropathy. This is also the most painful type of neuropathy. It affects all extremities,

most often the feet and the legs. Therefore, preventative management strategies seem to be the essential issue to be dealt with when considering neuropathy until more can be understood about the pathophysiology.

Microvascular disease has a characteristic thickening of the capillary basement membrane. (Dunn, Petri, & Raskin, 1980) This thickening can emerge over a period of 1-2 years. The thickening eventually results in decreased tissue perfusion (passage of fluids through the vessels). In this case, the severity of the disease has not been linked with the development of the thickening of the basement membrane. The frequency to which these lesions develop does appear to be associated with the duration of the disease.

Hypoxia (diminished availability of oxygen to the tissues) and ischemia (deficiency of blood due to functional constriction or actual obstruction of a blood vessel) of various organ often occurs from microangiopathy. (Arky, 1983) The two areas most often affected are the retina and the kidneys. Retinal ischemia has different stages and can develop in both IDDM and NIDDM. It is a progressive process that can result in retinal detachment or hemorrhage in the eye. If the ischemia occurs near the fovea in the eye, severe loss of vision may result which could lead to inevitable blindness. With regards to the kidney, it loses its ability to metabolize insulin along with other renal functions because of the thickening of the glomerular basement membrane. This eventually leads to complications which may lead to kidney failure. This is more common in IDDM than in NIDDM.

Macrovascular disease is the most prominent, overall cause of morbidity and mortality among individuals with NIDDM. Unlike microvascular disease, macrovascular disease is unrelated to the severity of the disease. It can be seen even in those with merely an impaired

glucose intolerance.

Macrovascular disease, often referred to as atherosclerotic disease, is a condition characterized by degeneration or hardening of the walls of the arteries and sometimes the valves of the heart, related especially to the thickening of the walls of the arteries. Changes in the vessel walls consist of deposits of platelets, smooth muscle cells, lipids, cholesterol, and calcium. Although this occurs in both the diabetic and the non-diabetic, it is quantitatively greater in the diabetic person.

Other important differences between the diabetic and the non-diabetic are very common for this disease process. The atherosclerotic disease is more common among diabetics. It appears at a younger age, progresses more rapidly, and is almost as common in women as it is in men. In the non-diabetic, the disease is more common in men than in women.

Other important differences include the vessels involved and the extent of the involvement. In the diabetic, more vessels are affected with a greater severity than in the non-diabetic. There is an increased incidence of peripheral vascular disease among diabetics. It is often the cause for amputation of the extremities.

The prevalence for coronary heart disease (CHD) is high among diabetics. In the coronary arteries of patients with diabetes, there appears to be a greater narrowing of the left main coronary artery, a greater number of major coronary arteries involved, and a greater dispersement in the distribution of the atherosclerotic lesions. (Beamish, Dhalla & Pierce, 1988) Diabetics with NIDDM account for the majority of cases of atherosclerotic disease. However, it is not limited to this type.

In general, the prevalence of the known major risk factors for CHD is amplified in

diabetics. The major risk factors that are of particular importance are lipoprotein concentration and composition (dyslipidemia), hyperinsulinemia, hypertension, and obesity.(Nieman, 1995) CHD in diabetic patients is associated with increased cholesterol levels in the blood, with reduced high density lipoprotein cholesterol (HDL) in NIDDM patients, and with increased triglyceride levels.

The most common lipid abnormality is increased triglycerides due to excessive concentrations of very low density lipoprotein cholesterol (VLDL). Triglycerides is related, in part, to the degree, duration, and control of the diabetes. The level of triglycerides in the blood plasma has been shown to decrease and return to normal levels after intensified insulin treatment.

In patients with NIDDM, HDL levels are reduced along with the increase in triglycerides. HDL is a form of cholesterol that helps to combat the onset of CHD and are thought to be a protective mechanism. Research has shown that the level of HDL-cholesterol was inversely related to CHD. Therefore, it would be beneficial to have a high level of HDL-cholesterol.

Another risk factor that is associated with CHD and diabetes is hypertension. Hypertension is more widespread among those people with IDDM and NIDDM. In NIDDM, hypertension can occur as a part of a syndrome in which it can coexist with obesity, insulin resistance, and dyslipidemia. It is thought that hypertension may be a result of the resistance in the blood vessels of diabetic patients. It has also been speculated that due to the mechanism of the disease there is an increase in extracellular fluid and sodium which contributes to hypertension.

Hypertension has been associated with nephropathy. Researchers are still not certain as to how hypertension is involved in the pathogenesis of nephropathy or if it is involved at all. It

is clear, however, that nephropathy accelerates hypertension and that hypertension accelerates the nephropathy.

NIDDM is most commonly associated with obesity, and obesity has also been linked to hypertension. There are many factor that correlate hypertension, obesity, and diabetes. High blood pressure is three times as common among the obese than it is in people who are not obese. In addition, diabetes is nearly three times as high among the obese. This is yet another reason that diabetics have an increased incidence of coronary heart disease.

Effects of Exercise

Physical activity is now establishing a place in the world of health. The list of the benefits of exercise is constantly lengthening. Research is still being performed that is showing the benefits of regular physical activity on diabetes and more specifically, on glucose control. Along with proper diet and weight reduction, exercise is being recommended for the management of diabetes, especially NIDDM.

Exercise has long been seen as helpful in controlling NIDDM. The major effects of exercise on NIDDM include the lowering of insulin levels after exercise, increasing HDL-cholesterol levels, and increasing sensitivity to insulin.(Arky, 1983) It appears that decreased pancreatic secretions of insulin result in the lower insulin levels. Glucose utilization is enhanced by exercise and thus the level of glucose in the body drop. This drop is often seen even after the exercise is discontinued.

Insulin sensitivity in the cells is lost with the onset of NIDDM. Exercise has been found to increase the sensitivity to insulin due to the decrease in insulin production. However, this exercise must be constant to produce an improvement in the insulin sensitivity. It has been shown

that the advantage is rapidly lost if the exercise is discontinued. Each exercise session leads to an improvement in insulin sensitivity that has been shown to last for one to two days. This can be quickly canceled by two days of no physical activity. Therefore, regular physical activity is needed in order to maintain the augmented insulin sensitivity. In both IDDM and NIDDM, insulin supplementation may need to be decreased as the duration of exercise increases. In the NIDDM, the insulin treatments are more likely to be discontinued due to this increased sensitivity to insulin. In addition to this, long term diabetic control is more likely to occur with NIDDM than with IDDM.

Regular aerobic exercise not only affects insulin and glucose levels, but it also reduces obesity. By reducing one of the factors that contributes to NIDDM, there is a greater chance that the disease can be controlled. It has been shown many times that a reduction in weight to a desirable level correlates with a decrease and sometimes a halt to the symptoms of NIDDM. This only stresses the importance of regular aerobic activity for a diabetic person.

Conclusion

With proper diet, aerobic exercise, and proper medical attention diabetes can be controlled. It is when the symptoms are ignored that problems arise with a greater frequency and severity. All problems can not be avoided, as they can happen to the most controlled case. Yet, it can only add to the life expectancy of the diabetic if these are understood and considered. In an effort to enhance this knowledge of patients on a general level I have addressed some of the major points of this serious disorder. It is still a wise idea to investigate any disease in an order to understand how it is going to effect you. With this in mind, it can be dealt with more thoroughly.

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